

Clinical review

Recent advances

Rheumatology

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The health consequences and fiscal burden of musculoskeletal diseases has been acknowledged but never fully addressed. An agenda unveiled by the World Health Organization to redress the balance sets specific goals for the next 10 years (the bone and joint decade). These include a 25% reduction in the expected increase in morbidity from rheumatoid arthritis, osteoporosis, and osteoarthritis.

Methods

We have reviewed advances in rheumatology that can be easily integrated into routine clinical practice and highlighted areas where appropriate treatment has been shown to prevent later disability or morbidity. References are supplied for published trials and systematic reviews.

Osteoarthritis

The chronic disease model of illness advocates patients as managers of their disease. In a trial to assess this model in 211 patients with osteoarthritis of the knee, Mazzuca et al reported greater benefits over one year in a self care group compared with standard treatment.¹

Diet

Cross sectional studies and studies of longitudinal cohorts have shown that obesity increases the risk of osteoarthritis of the knee in both men and women,² primarily by increasing forces across the knee. An imbalance of growth factors affecting the cartilage and underlying bone may also contribute. Weight loss reduces symptoms as well as improving functional ability.³ High vitamin C intake is associated with a threefold reduction in progression of osteoarthritis of the knee.⁴ Progression of osteoarthritis of the knee and hip is faster in people with lower vitamin D concentrations.^{5,6} However, as yet there is no evidence that vitamin supplementation improves symptoms.

Physical activity

Previous knee surgery and injury are risk factors for osteoarthritis of the knee, as are occupational kneeling and squatting. Observations in the Framingham heart cohort confirm that heavy physical occupational and leisure activity, particularly in obese people, predispose to subsequent osteoarthritis of the knee.⁷

Coordinated joint movement requires integration of afferent nerves from muscle intrafusal fibres and

Recent advances

Weight loss of even a few kilograms improves symptoms of osteoarthritis

Quadriceps exercises are beneficial in patients with osteoarthritis of the knee

Gastroprotective and cyclo-oxygenase-2 selective drugs reduce the incidence of ulcers

Early use of antirheumatoid drugs improves outcome and slows joint destruction

Patients at risk of osteoporosis can be identified easily

The wider range of preventive treatments for osteoporosis should help ensure long term compliance

receptors for joint proprioception. It is not known if impaired input from both is a cause or consequence of osteoarthritis of the knee. Exercise based rehabilitation may improve neuromuscular control. Reduced pain and improved function and quality of life were found after exercises to strengthen quadriceps.^{8,9}

Complementary therapies

Chondroitin and glucosamine are marketed as food supplements and have been advocated for joint pain in the media. The absence of side effects makes them attractive therapies. A meta-analysis showed short term evidence of benefit,¹⁰ and a three year randomised placebo controlled trial found less radiographic progression of osteoarthritis of the knee in people taking glucosamine.¹¹

Several studies report improvement in symptoms from acupuncture as adjuvant therapy for osteoarthritis of the knee.¹² Although these studies did not use a placebo group, this criticism applies equally to trials of many elective surgical procedures.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs are the most commonly prescribed drugs in the management of

rheumatic disease. Gastrointestinal ulcers occur in 15-20% of patient taking non-steroidal anti-inflammatories, 70% of them in the stomach. Around 2-4% of patients develop ulcer related complications, mainly bleeding and perforation. Women, especially those aged over 70 years with coexisting cardiac disease and previous peptic ulcers, are at greatest risk. These risk factors are additive.

Options to prevent complications include H_2 receptor antagonists, proton pump inhibitors, and misoprostol. More recently, selective and specific cyclo-oxygenase-2 inhibitors have become available. A two part comparative study of omeprazole and misoprostol in patients taking non-steroidal anti-inflammatory drugs found that omeprazole healed more gastric and duodenal ulcers than misoprostol. In the maintenance phase omeprazole prevented more duodenal ulcers than misoprostol but not gastric ulcers. No comment on ulcer related complications can be made.¹³

Two cyclo-oxygenase isoforms are recognised: cyclo-oxygenase-1 is fundamental to normal function (expressed in the gastrointestinal tract, kidneys, and platelets), whereas cyclo-oxygenase-2 is induced during inflammation. Two specific cyclo-oxygenase-2 inhibitors are currently available, rofecoxib (licensed for osteoarthritis only) and celecoxib (licensed for osteoarthritis and rheumatoid arthritis). Both are as effective as conventional non-steroidal anti-inflammatory drugs in arthritic patients.^{14 15} Dyspepsia occurs in similar numbers of patients as with conventional non-steroidal anti-inflammatories. The incidence of endoscopic ulcer with cyclo-oxygenase-2 inhibitors, however, is similar to that in the placebo group.

To examine the issue of ulcer related complications, Langman et al conducted a pooled analysis of eight studies comparing conventional non-steroidal anti-inflammatory drugs with placebo and rofecoxib in patients with osteoarthritis (total sample size, 5435).¹⁶ Although the number of complications (perforation, painful ulcer, and bleeding) was small, fewer arose with rofecoxib than with other non-steroidals (ibuprofen and diclofenac; no complications were attributed to nabumetone but numbers treated were small).¹⁶

Rheumatoid arthritis

Early disease modifying antirheumatic treatment improves subjective and objective markers of severity of rheumatoid arthritis—that is, joint pain, swelling, and tenderness; duration and severity of morning stiffness; patient wellbeing and function; and inflammatory markers such as erythrocyte sedimentation rate and C reactive protein. Early treatment also improves outcome measures such as disability, quality of life, and radiological progression.¹⁷

Advances have focused on defining when treatment should begin, how long to continue, if one drug is better than others, if combinations confer additional benefit, and the evidence for the more expensive biological drugs. The double edged sword of oral corticosteroid treatment remains under scrutiny 50 years after its introduction by Hench et al.¹⁸

When should treatment be started?

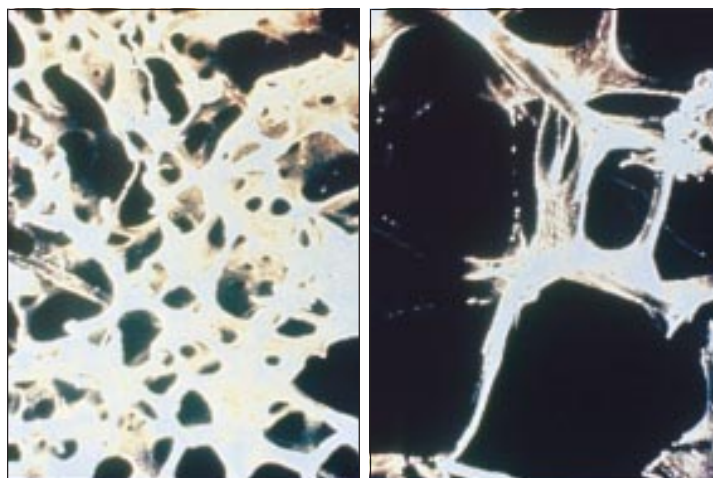
Four recent studies emphasised the importance of early treatment for maximum benefit and to reduce future disability. Two retrospective analyses showed patients treated early were more likely to maintain vital functional benefit at five years.^{19 20} An open randomised controlled trial in 238 consecutive patients allocated to immediate or delayed introduction of disease modifying treatment found that the group given immediate treatment had significant advantages in functional disability, patient score, and radiological progression at one year.²¹ The fourth study in 199 patients reported better pain and physical outcomes at three years for patients given early treatment compared with patients in whom treatment was delayed for nine months.²²

Is it necessary to continue treatment once a response is achieved?

A study of 285 patients who had shown a sustained response to disease modifying treatment over five years found that more flares occurred in the group randomised to placebo than in those who continued the drug over one year.²³ This finding was confirmed by a study that randomised 112 patients to treatment or placebo. Flares occurred in 42 patients, 33 of whom were in the placebo group. Fifty two people refused to participate because they did not wish to be exposed to the chance of receiving placebo.²⁴ These results show that treatment is effective, of greater benefit if introduced early, and needs to be sustained indefinitely.

Which drug to use? How much benefit should be expected?

Sulfasalazine and methotrexate are widely used anchor drugs. Intramuscular gold and penicillamine are more toxic than the other drugs, and hydroxychloroquine and auranofin confer less benefit. The future roles of leflunomide (a recently introduced immunomodulatory drug that inhibits synthesis of pyrimidine and has a similar benefit to sulfasalazine and methotrexate)²⁵ and minocycline (effective in rheumatoid arthritis but not licensed) have yet to be established. Concerns about long term cumulative toxicity with systemic corticosteroids and the short term relief of symptoms (average nine months) has limited their widespread use, despite favourable radiological data.²⁶ In the com-



Normal (left) and osteoporotic (right) trabecular bone

bination study by Boers et al, the dose of corticosteroid (60 mg) was too high to be maintained without unacceptable toxicity.²⁷

Along with drugs against tumour necrosis factor α , the choice of antirheumatic drugs is now wider. Thus all patients with rheumatoid arthritis should have access to an effective drug early in the course of their disease. A 50% improvement in symptoms and acute phase reactants should be achieved.

Targeted immunotherapy

Tumour necrosis factor α , a product of macrophages, acts on the immune system to induce the production of other pro-inflammatory mediators. Two drugs that inhibit tumour necrosis factor activity have recently been licensed for treatment of rheumatoid arthritis, infliximab and etanercept. Infliximab is a chimeric monoclonal antibody given as an intravenous infusion at 0, 2, and 6 weeks and then every 8 weeks. Infliximab cross links tumour necrosis factor bound to T cells, thus inactivating or destroying it. A double blind study of infliximab in addition to methotrexate showed considerable benefit. Side effects include short lived early and late infusion reactions. One patient receiving infliximab died of infection during the study.²⁸

Etanercept is a tumour necrosis factor receptor fusion protein designed to bind circulatory tumour necrosis factor α . It is given as a subcutaneous injection of 25 mg twice weekly, either alone or with methotrexate. Results from placebo controlled studies are encouraging.²⁹ Although no major complications were seen in clinical trials, serious and fatal infections have been reported during postmarketing surveillance in the United States.

Current limitations of treatment

There are concerns that continued inhibition of pro-inflammatory molecules may increase the risk of infection and cancer, particularly lymphoproliferative malignancies. Currently there is no such evidence. Unless these drugs prove more effective than existing treatments, their greater costs may preclude widespread early use.

Osteoporosis

Osteoporosis is an important health problem in Western nations, and the ageing population is likely to exacerbate the problem.³⁰ An estimated 75 million people in Europe, the United States, and Japan are affected by osteoporosis. The resultant fractures have associated economic costs and a substantial impact on quality of life. Vertebral and hip fractures are associated with extensive morbidity and premature mortality. Indeed, even the fear of falling in older women affects wellbeing; recognition that osteoporotic fractures often lead to loss of ability to live independently has a detrimental effect on quality of life.

Who to target?

A third of women and one in eight men will sustain an osteoporotic fracture. In childhood adequate diet and weight bearing exercise are essential to achieve optimal peak bone mass. The box lists some of the actions that can be taken by adults to prevent osteoporosis.

The patients most in need of assessment can be fairly readily identified: those who have sustained a low

Osteoporosis: what can the patient do?

Stop smoking

Exercise—Weight bearing exercise improves bone density, and activities such as swimming are important in maintaining mobility and preventing falls

Diet—An adequate calcium intake (1000 mg till age 60, 1500 mg thereafter)

Ongoing research studies

Osteoarthritis: effects of glucosamine and chondroitin on outcome (National Institutes of Health study)

Non-steroidal anti-inflammatory drugs: do cyclo-oxygenase-2 selective drugs reduce gastrointestinal toxicity in "true to life" setting?

Rheumatoid arthritis:

Value of combination treatments

Role of targeted immunotherapy

Osteoporosis:

New methods of delivery of bisphosphonates including nasal inhalation

Role of combination treatments

impact Colles' or other fracture are at increased risk of subsequent serious osteoporotic fracture. Other risk factors include smoking, low weight (body mass index < 19), early menopause, immobility, corticosteroid treatment, and maternal family history.

An audit found that most patients who have an osteoporotic fracture are not started on treatment for secondary prevention of osteoporosis.³¹ Recent guidelines on the prevention and management of corticosteroid induced osteoporosis have outlined a practical approach for this group of patients.³²

Range of treatments

Prophylaxis against osteoporosis needs to be continued long term. The side effects and method of administration must therefore be acceptable to the patient if compliance is to be optimal. Thus the increasing range of treatments and the greater acceptability of these options are important. These include "no bleed" hormone replacement therapy and selective oestrogen receptor modulators.³³ Selective oestrogen receptor modulators do not increase the risk of breast cancer and may prove protective. A wider range of bisphosphonates is available (with alendronate showing particular benefit in relation to femoral neck fracture),³⁴ but gastrointestinal intolerance poses a problem.³⁵ More palatable calcium and vitamin D preparations with appropriate doses of each have been formulated. Supplementation has been shown to reduce hip fractures in elderly people³⁶ and is also advisable in patients with low calcium intake and evidence of osteoporosis. Many millions of patients have the potential to benefit from an appropriate osteoporosis prevention strategy.

The recent observation that inhibition of hydroxymethylglutaryl coenzyme A reductase may reduce the risk of fracture raises the possibility that patients requiring statin for cardiovascular disease may derive additional benefit in terms of osteoporosis.³⁷

Competing interests: None declared.

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A memorable patient All in a day's work

At 82 she was still a beautiful woman. Her numerous medical problems and her elbow crutch did not diminish her elegance and her speech, polished by some high class English boarding school for girls as well as the years spent being the gracious hostess at colonial garden parties.

I gradually got round to the reason for her seeing me for a cardiologist opinion. Chest pain? Well, yes, particularly on hills. But I needed to know the extent to which she might be limited around the house. I asked my usual question, "What would be the heaviest thing you would do in an ordinary day at home?"

There was a pause during which I seemed to hear the regular gentle swish of the punkah and the steady buzzing of the cicadas in the sandalwood trees. "I suppose it is when I carry my tortoises about."

There was a moment or two while my imagination raced. I tried a nonchalant, "And how much would a tortoise weigh, may I ask?"

"Well Stanley is 21 pounds, while Cynthia is rather less as she had to have some facial surgery after a mishap with a lawn mower."

It was all terribly British. Not a smile cracked. At the end she said, "I do hope you might come and meet Stanley and Cynthia sometime."

Honours come no higher.

(The names of the tortoises have been changed.)

Edwin R Nye *physician, Dunedin, New Zealand*

We welcome articles of up to 600 words on topics such as *A memorable patient*, *A paper that changed my practice*, *My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.